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ORAL HEALTH IN PATIENTS WITH CROHN´S DISEASE

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ORAL HEALTH IN PATIENTS WITH CROHN´S DISEASE

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“One never notices what has been done;

one can only see what remains to be done.”

Marie Skłodowska-Curie

With love to Anna & Anton

ABSTRACT

Dental caries and periodontal diseases are the most common oral diseases worldwide. They are multifactorial diseases which include several risk factors. Dental caries causes tooth ache and tooth loss, with numerous risk factors are such as cariogenic bacteria, decreased salivary flow, poor dietary habits, increased sugar consumption, and neglect of oral hygiene. Periodontal diseases, including gingivitis and periodontitis, are inflammatory processes of the gingiva and supporting structures of the teeth and is characterized by destruction of the tissues and eventually tooth loss. Risk factors for periodontitis result from a combination of genetic factors and environmental factors such as poor oral hygiene, amounts of periopathogenes, smoking and systemic diseases. Crohn´s Disease (CD) is a granulomatous chronic inflammatory disease that can affect the whole gastrointestinal tract, although it is usually localized to small and large intestine. There is no cure for CD. The aetiology of CD is poorly understood but an interaction between genetic, microbial and environmental factors may participate in the development and progression of CD.

The general hypothesis of these studies was that patients with CD have poorer oral health than people without CD. The present thesis includes three studies which all aim to investigate oral health in patients with CD.

Study I is based on a questionnaire, including 1598 patients with CD and a randomly selected control group of 1000 subjects. *Study II* and *III* are the clinical studies comprised of 150 patients with CD and a control group comprising of 75 subjects.

The first specific aim was to investigate how patients with CD perceived their oral health compared to control group *(Study I).* Secondly we wanted to find out in a clinical study if CD patients had a higher prevalence and risk for dental caries *(Study II).* The third aim was to investigate whether CD patients had a higher prevalence and severity of periodontal disease compared to controls without CD *(Study III).*

The main findings of all these studies revealed that patients with CD perceived their oral health to be poor *(Study 1)*. Patients who had undergone resective surgery had a significantly higher DMF-S score *(Study II)* and CD patients had significantly more dental plaque and gingival inflammation *(Study III*). There were more smokers in the CD group when compared to the controls *(Study I, II & III).*

Furthermore, our results in *Study I* reported that CD patients had a greater need for dental treatment and there was a correlation between more severe forms of CD and oral health. This group also reported more mouth and tooth related problems. *Study II*, showed that men in the

CD group had significantly more decayed teeth decayed surface and more dental plaque when compared to CD women. The results in *Study III* showed that the percentage of CAL≥3 was higher in patients than controls which indicates that they had a greater prevalence of periodontitis. No differences in radiographic bone loss was observed between CD patients and controls. However, men in the CD group had significantly more BOP, CAL, alveolar bone loss and higher prevalence with periodontitis compared to women in the same group.

In conclusion, the findings in this project indicate that CD patients and especially men had a poorer oral health, more caries, dental plaque, BOP and CAL. Thus, our finding confirmed our hypotheses. There is a need to develop an oral care program, which include the prevention of oral disease, support and motivation to take care of the oral hygiene, as well as smoking cessation.

Keywords: Crohn´s disease, oral health, questionnaire, DMFT, DMFS, dental caries, dental plaque, sugar consumption, inflammation, BOP, periodontal disease, PPD, CAL, BOP, inflammation

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. **Rikardsson, S**., Jönsson, J., Hultin, M., Gustafsson, A. & Johannsen, A. (2009) *Perceived oral health in patients with Crohn's disease.* Oral Health Prev Dent 7, 277-282.

II. **Szymanska, S**., Lördal, M., Rathnayake, N., Gustafsson, A. & Johannsen, A. (2014) *Dental caries, prevalence and risk factors in patients with Crohn's disease.* PLoS One 9, e91059. doi:10.1371/journal.pone.0091059.

III. **Szymanska, S**., Lördal, M., Croonqvist-Gierestam, C., Gustafsson, A. & Johannsen, A. (2015) *Prevalence and severity of periodontal disease in patients with Crohn´s disease.* Submitted.

CONTENTS

LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BOP	Bleeding on probing
CAL	Clinical attachment level
CAJ	Cemento-enamel junction
CD	Crohn´s disease
DMF-S	Decayed, missed, filled surface index
DMF-T	Decayed, missed, filled teeth index
DS	Decayed surface
DT	Decayed teeth
FS	Filled surface
FT	Filled teeth
IBD	Inflammatory bowel disease
LB	*Lactobacilli*
MS	Missing surface
MT	Missing teeth
NRS	Not resective surgery
OR	Odds ratio
PPD	Probing pocket depth
VPI	Visible plaque index
RS	Resective surgery
SCB	National Statistics Organization
SD	Standard deviation
SM	*Steptococcus mutans*
TNFα	Tumor necrosis factor alpha
WHO	World Health Organization
IL-1β	Interleukin 1β
IL-6	Interleukin- 6
LPS	Lipopolysaccharides

TNF-α	Tumor necrosis factor- α
MMPs	Matrix metalloproteinases
PGE2	Prostalandin E2

1 INTRODUCTION

1.1 PERIODONTAL DISEASE

Periodontal disease gingivitis and periodontitis are some the most prevalent chronic inflammatory conditions causing severe major public health problems worldwide [1].

1.1.1 Gingivitis

Gingivitis affects up to 90% of the population [2], being the first manifestation witch is an inflammation of gingival soft tissue predominantly initiated in response to pathogenic microflora in the dental plaque adherent to tooth surfaces. Clinical signs of gingivitis are characterized by swelling, bleeding and redness (Figure 1) [3, 4]. Gingivitis can be reversed if the biofilm is disrupted and adequate plaque control maintained [5, 6] . However, if left, untreated gingivitis can progress to destructive chronic periodontitis, involving breakdown of the tooth-supporting structures [7].

Figure 1. Gingivitis. Inflammation of gingival soft tissue, characterized by swelling, bleeding and redness.

1.1.2 Periodontitis

The prevalence of periodontal disease varies in different parts of the world from 13-57 % whereas severe periodontitis impacts about 5-20 % of population worldwide [8-15]. Periodontitis is more advanced inflammation than gingivitis that is usually asymptomatic in the early phases and becomes uncomfortable and painful in periods when the disease progresses (Figure 2).

Periodontatis occurs when the inflammation extends into the tissue and leads to non-reversible breakdown of the tooth supporting tissues, and alveolar bone loss [16-18]. Finally, periodontitis left untreated, may lead to tooth loss and have an impact on quality of life [16-18] .

Figure 2. Periodontitis. Advanced inflammation extend into the tissue.

Some studies suggest that the surface area of inflammation in periodontal pockets may range from 8 to 20 cm² in moderate periodontitis and 50 to 72 cm² in severe peroidontitis. In subjects with no periodontitis the surface area of periodontal pockets accros all tooth has been suggested to be 5 cm² [19-21]. Periodontitis is a multi-factorial disorder, which is influenced by genetic and environmental risk factors [1, 17, 22]. Age, gender, and ethnicity are important non- modifiable factors for periodontitis, as well as the individual´s susceptibility [22]. However, possibly modifiable risk factors are social and behavioural factors, income, education status and smoking. Cigarette smoking is strongly associated with both prevalence and severity of periodontitis [22-25]. It has been estimated that 75% of periodontal disease cases amongst current smokers were related to smoking and 50 % to former cigarette use [26]. Furthermore, the associations between periodontitis and psychosocial stress have been proposed [27]. Behavioural factors are a key component to prevention of periodontal diseases enhancing the patient's motivation, therefore motivational interviewing might be one appropriate methodology for this [5, 6].

Associations have also been identified between periodontitis and systematic risk factors for example diabetes mellitus, obesity, hypertension, cardiovascular diseases and other chronic diseases characterised by underlying systemic inflammation [14, 27].

Chronic periodontitis is diagnosed by clinical examination and study of x- images. The disease is divided into *Localized periodontitis*, when up to 30 % of teeth are affected and *Generalized periodontitis*, if more than 30 % of teeth are affected. Severity of bone

destruction is divided in three classes based on the size of attachment loss: slight 1-2 mm; moderate 3-4 mm and sever ≥5 mm [28] .

Periodontitis is an inflammatory disease and the pathogenesis complex involving interactions between bacterial products, host response, and inflammatory mediators, as well as environmental and genetic factors (Figure 3).

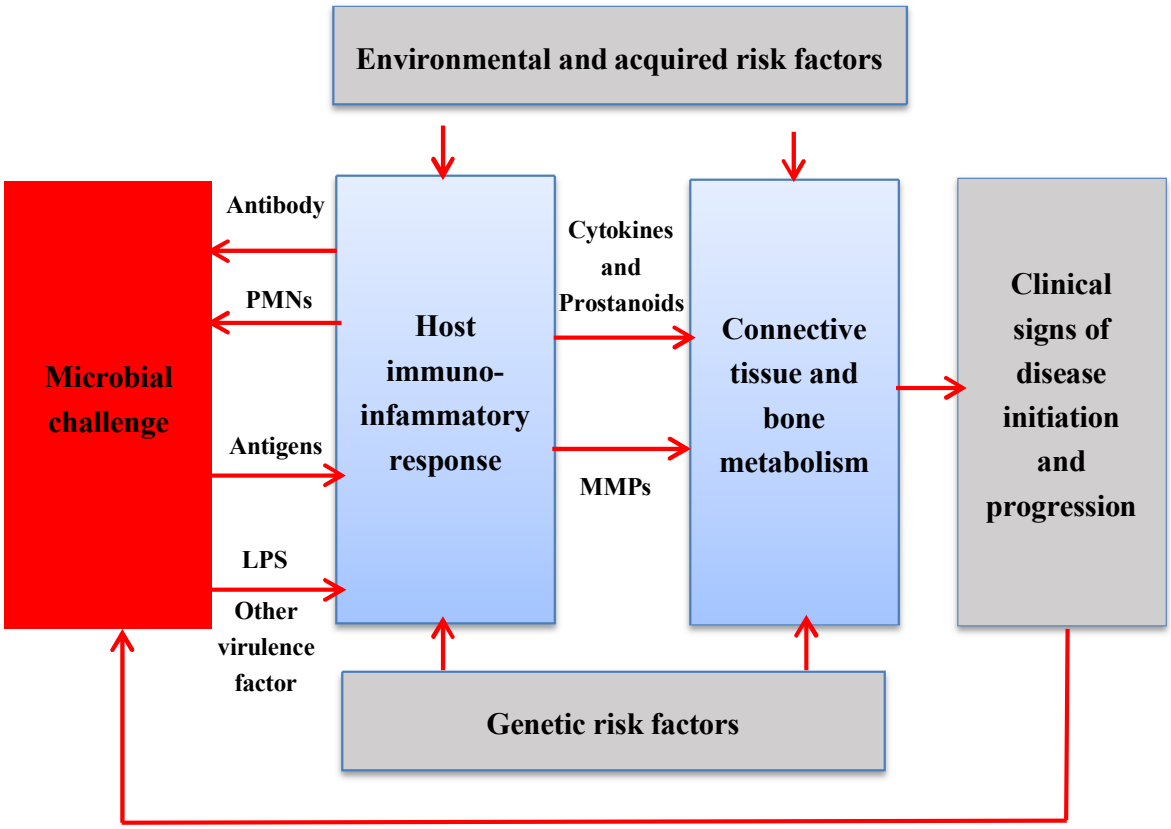


Figure 3. Schematic model of pathogenesis of periodontitis. PMNs- polymorphonuclears leukocytes; LPS- lipopolysaccharide; MMPs- matrix metalloproteinases. Adapted from Page and Korman 1997 [29].

There are over 700 bacterial species in the human oral cavity [30-32]. It is known that microbes from the oral cavity can cause oral infectious diseases, including endodontic infections, tonsillitis, caries and periodontitis. A number of studies show evidence associating oral bacteria to systemic diseases, such as diabetes, pneumonia, cardiovascular disease [33-37].

Periodontitis is initiated by the presence of bacteria on the tooth surface and in the gingival crevice [17]. The process starts when bacterial species in oral cavity adhere to each other and form a microbial biofilm on the tooth surface, first supragingivally in the gingival crevice and later subgingivally, forming a gingival pocket (Figure 4) [38]. Bacterial growth in the oral biofilm is influenced by the exchange of metabolites, chemical signals, and toxic products

that form a protective matrix helping to the development of periodontitis [39]. Oral bacteria accumulated on the tooth is primarily Gram-positive and include species of *Streptococcus* and *Actinomyces*.

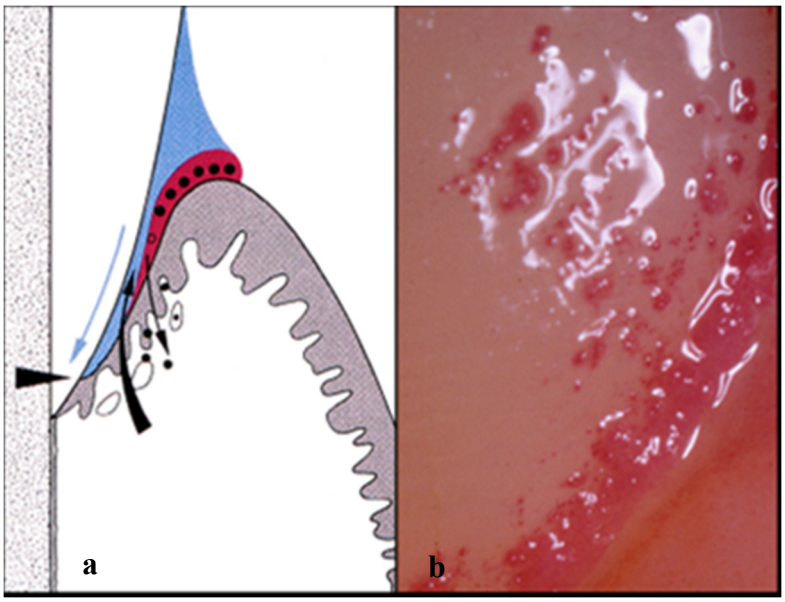


Figure 4. Plaque begins to form in the gingival sulcus and other protected niches of the tooth. (a) Destruction of collagen will occur as a direct result of microbial action through their release of toxins, lipopolysaccharides or enzymes. (b) Bacterial plaque forms as a biofilm in the gingival sulcus shortly after the cleansing of the tooth surface. Three-day-old plaque.
Reprinted with the permission from the publisher John Wiley & Sons [7].

Subsequently this matrix adopts to a more anaerobic, Gram-negative environment, which accumulates deeper in gingival sulcus [38, 40]. Periodontal pathogens, such as *Prevotella intermedia, Aggregatibacter actinomycetemcomitans* and the group named "red complex" including bacteria species *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* that become more prevalent in deep periodontal pockets and significantly linked to advanced periodontitis. These microorganisms stimulate an inflammatory response which can cause destruction of periodontal tissues in susceptible individuals [41]. Periodontal disease is not generally expressed in individuals with poor oral hygiene that harbor periodontal pathogens but the disease are also more involved in a susceptible host [42].

Chronic periodontitis starts with an infection initiated by pathogenic bacteria from the oral biofilm. Microbial products, such as proteases, lipopolysaccarides (LPS), metabolic and other toxic product in sulcus attack the host defence mechanisms and modify immune responses. This microbial challenge induces a host -mediated tissue destructive immune response [43-45]. The inflammatory responses activate immune cells such as neutrophils and

macrophages/monocytes, which are primary protective components of the first-line defence [16, 44].

In periodontitis the microbial challenge continues and LPS from Gram negative-bacteria stimulates inflammatory mediators e.g., macrophages/monocytes, neutrophils and T-lymphocytes to produce proinflammatory cytokines including TNF-α (tumor necrosis factor-α), IL-1β (Interleukin-1β), IL-6 (interleukin-6), PGE2 (prostaglandin E2) and matrix metalloproteinases (MMPs), which play a significant role in the damage of tissue and periodontal bone resorption [16, 29, 44]. Although, some of bacterial components can initiate periodontitis it is important to consider various risk factors such as cigarette smoking and heredity with outweigh the disease occurs and the severity of clinical outcome [22, 25].

1.2 DENTAL CARIES

Dental caries is a major public health problem worldwide in most industrialized countries and causes tooth pain and tooth loss. People are predisposed to this chronic disease thought their lifetime but studies show that caries progression slow down with increased age [46]. In general caries, prevalence and severity has decreased in high-income countries over recent years [47, 48]. However, in low-income countries dental caries continues to increase amongst people with low education and socioeconomic status, and absence of oral health care service, poor lifestyles and elderly [49-52].

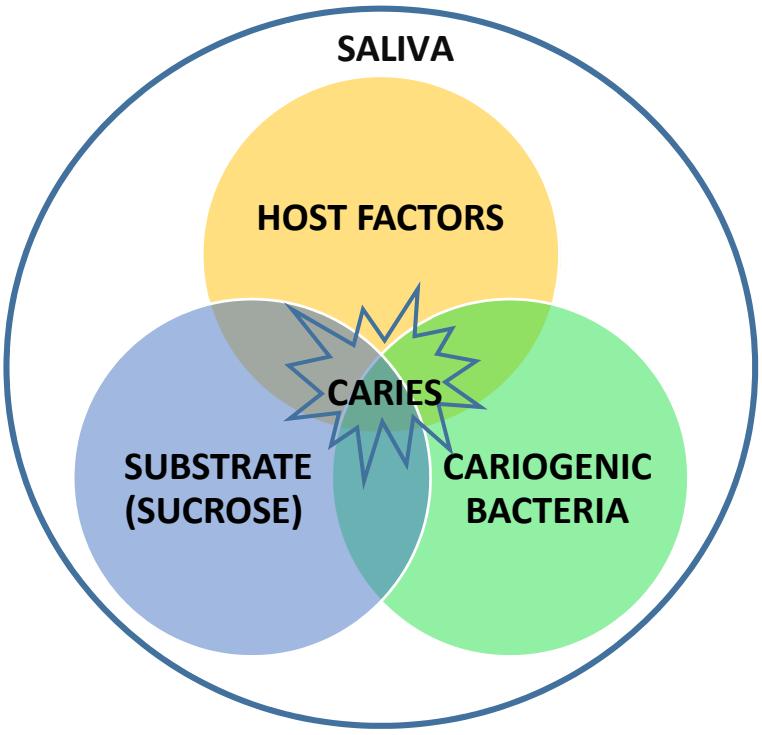


Figure 5. Factors that interact to form dental caries. Adapted from Krol 2003[51]

Miller (1890) was the first to demonstrate the bacterial invasion of dentinal tubules of both carious and non-carious dentin association with lactobacilli-dentinal caries was reported by Goadby in 1899 [53]. However, it was not until the late 1950 s that experimental evidence clearly established the fundamental role of these bacteria in dental caries [54]. They are now considered secondary invaders rather than initiators of the caries process [55].

Established risk factors are now include increase of cariogenic bacteria, decreased salivary flow, insufficient oral hygiene, poor dietary habits such as increased sugar consumption, consumption of soft drinks, as well as socioeconomic factors [51, 56-59]. Dental caries define both caries lesion and caries process [60, 61]. Cavity, or decayed surface is a drastic result from interactions over time between bacteria, a substrate and host factors that include teeth and saliva (Figure 5) [51, 61]. Dental caries is a multifactorial disease that starts with changes inside the biofilm/dental plaque and is affected by salivary flow and composition, exposure to fluoride, consumption of dietary sugars, and by preventive behaviors. A systematic review supports a relationship between the amount of sugars consume and dental caries development [62]. A 4-year prospective study, reported that consumption of sugar-sweetened beverages on a daily basis will lead to greater caries risk in adults and that such risk will increase even further with increasing frequency of daily consumption. An association was consistent across socio-demographic characteristics [63].

Endogenous bacteria in the biofilm mostly *Lactobacilli* and *Mutans streptococci*, such as *Streptococcus mutans* and *Streptococcus sobrinus* produce acid a by- product of metabolism of fermentable carbohydrates [64]. *Streptococcus mutans* exemplifies the cariogenic properties of sucrose metabolism, acidogenicity via fermentation, and adherence and biofilm formation via synthesis of extracellular glucans [65]. Studies have described the relationships between the rate of high intake of medication, subjective feeling of dry mouth, saliva flow, saliva composition and the salivary level of lactobacilli in adults. Clearly, lactobacilli play a significant role within the oral ecosystem whether oral health or carious diseases [66-69].

Caries lesions develop when the acids as by-product from metabolism of fermentable carbohydrates, causes the local pH value to decrease below a critical value resulting in demineralization and destruction of hard tooth tissues. If the diffusion of calcium, phosphate and carbonate out of the tooth is allowed to continue, cavitation will eventually take place. Caries demineralization can be reversed and stopped in its initial phases through uptake of fluoride which supports the circulation of calcium and phosphate into the tooth, allowing remineralisation of the crystalline structures in the lesion and rebuild surfaces of fluoridated hydroxyapatite and fluorapatite. Saliva acts as a buffer and restores pH in the biofilm. If dental caries stops, progresses or reverses over time is dependent on the balance between demineralization and remineralisation and without proper oral hygiene can develop, spread into the dental pulp and destroy the tooth [70, 71].

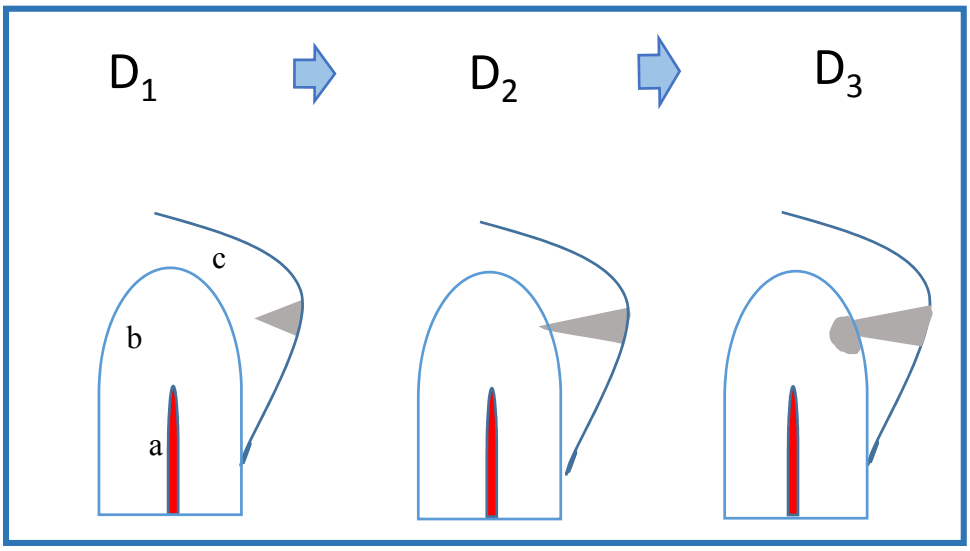


Figure 6. Schematic model of approximal caries. a- pulp; b-dentin; c- enamel.

The caries disease can be seen on both the crown and root and it can affect enamel, dentin and cementum. Caries diagnosis includes visual and tactile examination with a dental probe, and detection of lesions on approximal surfaces with bitewings radiographs [72, 73]. Approximal caries categorized as enamel caries D_1, D_2 and D_3 as dentin caries (Figure 6). Dental caries experience indices in: tooth DMFT index (number of Decayed, Missing due to caries, and Filled Teeth in the permanent dentition) and surface levels DMFS index (number of Decayed, Missing due to caries, and Filled Surfaces in the permanent dentition). DMFT is divided into very low <5.0; low 5.0-8.9; moderate 9.0-13.9; high >13.9. DMFS [74, 75].

1.3 CROHN´S DISEASE

Inflammatory bowel diseases (IBD) are significant health problems worldwide that cover a variety of overlying clinical diseases characterized by chronic inflammation at different sites in the gastrointestinal tract. IBD, include collagenous, eosinophilic, lymphocytic and indeterminate colitis but most commonly are ulcerative colitis (UC) and Crohn´s disease (CD). UC causes inflammation in the large intestine and rectum, whereas CD can affect the whole gastrointestinal tract although mainly the large intestine, small intestine or both [76, 77].

CD was described in 1932 by American gastroenterologists, Burrill Bernard Crohn, Leon Ginzburg and Gordon D. Oppenheimer and since that time, the name of the disease has been connected with Dr. Crohn´s name and used in the literature. The author of the first Polish description of the disorder from 1904 was surgeon Prof. Antoni Leśniowski and in Poland the disease is known as Leśniowski-Crohn's disease out of the respect for this author´s contribution [78, 79].

The prevalence and incidence of CD varies around the world, with the highest rates in developed countries. CD is most common in Northern Europe and North America [80-84]. In Sweden, the prevalence is about 2 % and 5 to 7 individuals per 100,000 are diagnosed with CD every year [85-88]. The highest reported incidence of CD in Europe was 12.7 per 100,000 person and 20.2 per 100,000 person- a year in North America. The highest reported prevalence values for CD in Europe were 322 per 100,000 persons and North America 319 per 100,000 persons [80]. The incidence and prevalence of CD increases in the world both in industrialized and developing countries, and the disease seems to be emerging as a global disease [80, 81]. CD can occur at any time from childhood to late adulthood and both gender are likewise affected. This disorder is most commonly diagnosed before the age 40 but the numbers being diagnosed during their late teens and twenties is increasing [83, 89-91].

CD is characterized by episodes or flares with symptoms alternating with symptom-free phases, remissions. Typical symptoms during flares are abdominal pain, fatigue, fever and bowel obstruction with diarrhoea and rectal bleeding, significantly impairing quality of life [76, 92, 93]. Diagnosis of CD is based on history, clinical examination, endoscopy with biopsies and complementary histological, radiographic and laboratory findings [93, 94]. It has been suggested that CD starts as an inflammatory process and might develops over time to a more complex disease with stricture, fistula and abscess formation [92, 95, 96].

At present, CD therapies are aimed to reduce the inflammation during a flare, i.e. induce remission, and to prevent a new flare, i.e. maintain remission and progress of the most common symptoms, mainly abdominal pain. There are several pharmacological alternatives such as glucocorticosteroids, immunomodulators and biological agents. For some patients, for whom pharmacotherapy is inappropriate, or those not responding to pharmacotherapy surgical treatment is appropriate [93, 97-99]. Until recently, there has been no curative medication for CD and the drugs also cause several side effects. Surgery does not cure CD but in some circumstances it can be considered as a possible alternative to pharmacotherapy. Indications for surgery, include complex abscesses and fistulas, strictures with symptoms of bowel obstruction and cancer [100]. About 50 % of patients with CD have intestinal complication after diagnosis and need surgical treatment [101]. At 10 years follow up after resection of intestine has shown that about 30% to 50% of the patients require surgery, - or needed supplementary surgical treatment [90, 101-103].

Oral findings associated with CD were first described by Dyer et al. in 1969 [104]. Specific oral manifestations related to CD include frequent ulcerations, aphthous stomatitis, fissures, diffuse face- and lips erythema and hyperplasia in the mucosa. Hyperplasia is often found in combination with fistula and granuloma formation, which have the same histological form in the gastrointestinal tract. The frequency of oral manifestations in CD patients has varied between 0.5- 20% [105, 106]. Oral manifestations could be the first clinical feature of IBD. In

some individuals the oral manifestations occurred up to 10 years prior to presentation in the gastrointestinal tract [107-110].

The aetiology of CD is poorly understood but an interaction between genetic, microbial and environmental factors may participate in the development and progression of CD [77, 111-113]. A growing number of studies suggest the involvement of several genes in CD and IBD development but the contributions of genetic factors are complex [114, 115]. Some studies with monozygotic twins suggest hereditary for CD of between 20 to 50% [116-118]. Genetic factors are known to regulate the structure of the microflora [119] and in addition, a link between the microbiota and the lining of the gut mucosa has been proposed as possible aetiological environmental factors [111]. Several theories, mostly related to urban living, are possible, such as consumption of a Western civilization diet containing large amounts of refined sugar and dietary fats [113, 120-122] as well as stress [123, 124]. Hygiene hypotheses indicate that reducing microbiological variation and rising incidences of autoimmune disease [125]. Smoking worsens CD, reducing treatment responses and increasing the number of relapses and complications [126, 127]. However, the specific cause of the disease mains to be fully clarified [128].

2 AIMS OF THE THESIS

2.1 GENERAL OBJECTIVES

The general aim of this project was to test the hypothesis that patients with Crohn´s disease (CD) have worse oral health than people without CD. In the future the project also aims to provide new opportunities for support strategies for the prevention of oral disease in these patients who already suffer from a lifelong disease.

2.2 SPECIFIC OBJECTIVES

2.2.1 Study I

The aim of was to investigate perceived oral health of patients with CD in comparison with a control group with no CD in Sweden.

2.2.2 Study II

The aim was to test the hypothesis that patients with CD have a higher prevalence and risk for caries compared to people without CD.

2.2.3 Study III

The aim was to test the hypothesis that patients with CD have higher prevalence and severity of periodontal disease compared with controls without CD.

3 MATERIAL AND METHODS

3.1 ETHICAL CONSIDERATION

The research project conformed to the ethical principles for medical research in humans according to the recommendations of the Declaration of Helsinki. All subjects gave their written informed consent to participate. *Study I* did not need ethical approval in 2006. *Studies II* and *III* were approved by the Karolinska Institutet Ethical Research Board in Stockholm, Sweden, ref.nr. 2007/ 2:11, 2009/ 1953-32.

3.2 STUDY POPULATION

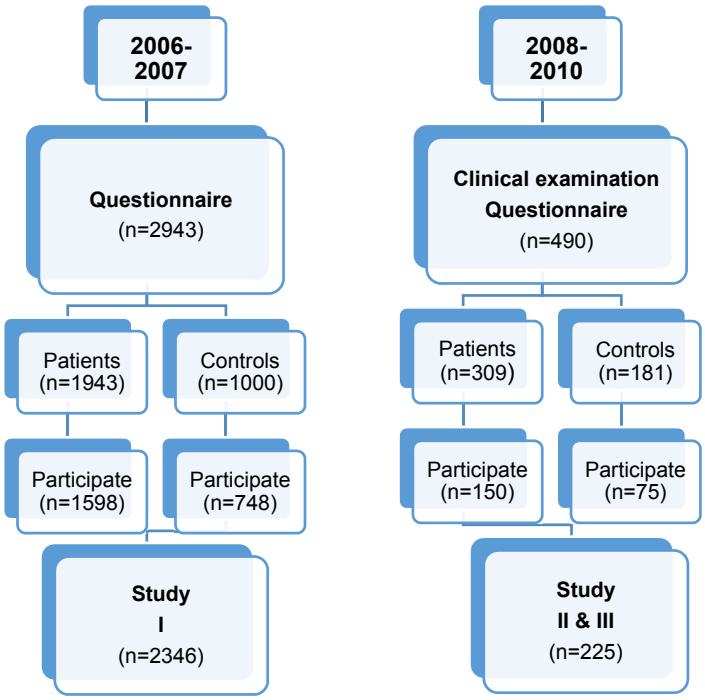


Figure 7. Flow-chart showing the selection of subjects from 2006 to 2010. Questionnaire from 2006-2007 was analysed and described in Study I. The clinical examination and questionnaire from 2008-2010 were analysed and descried in Studies II and III.

3.2.1 Study Population, Study I

3.2.1.1 Patients

A questionnaire was sent between autumn 2006 and spring 2007 to all members of Swedish Association of People with Stomach and Bowel Diseases with the diagnosis Crohn´s disease (CD). Totally, were 1943 questionnaires were sent to the patients and 1598 of them were returned. 68 % were women and 32% men, mean age 49. 7 years, who responded the questionnaire (Figure 7).

3.2.1.2 Controls

A randomly selected control group with 1000 subjects was chosen through National Statistics Organization in Sweden, SCB. The control group was matched to get the same age and gender as in CD group. 748 subjects who answered the questionnaires and 67 % of them were women and 33 % were men. The mean age of the controls was 49. 5 years.

The number of patients included was provided by the number of members in the patient organization who were diagnosed with the CD. 1000 controls were chosen to allow for an observed difference in perceived oral health of 10% with a power of over 90%.

3.2.1.3 Non-responders

345 CD patients and 252 controls without CD, of all subjects invited to participate in study declined and the reason was not asked.

3.2.2 Study population, Study II and III

3.2.2.1 Patients

Patients with diagnosis of CD, attending the outpatient clinic at the Department of Gastroenterology and Hepatology at Karolinska Hospital in Huddinge, between September 2008 and June 2010, were invited to participate in the study. 309 patients were asked to participate and 150 patients were enrolled, 73 females and 77 males, aged 18–77 years (Figure 7).

3.2.2.2 Controls

The control group was selected from 181 individuals that were randomly recruited through National Statistics Organization (SCB) in Sweden. 75 persons, 45 females and 30 males, accepted to participate in the study, aged 18–74 years. Selection of the control group was structured to achieve the same age and gender distribution as the patient group. All subjects were living in Huddinge community of Stockholm.

The number of CD patients (n =150) and the controls (n =75) was chosen to observe 10% differences of the population with a power of over 90%. Smaller differences were not clinically relevant. The power calculation was based on the differences reported by Brito et al. 2008 [129]. 150 CD patients and 75 controls would provide 80% power to detect a difference in means of DMFT of 2.8 between the groups (22%). The common standard deviation was 7.0, with a 0.05 two-sided significance level.

3.2.2.3 Non-responders

159 patients in the CD group and 106 individuals in the control group declined to participate in the study, though the reason was not asked. There was no statistical significance between

age and gender of the participants and those who did not participate by a comparative analysis.

3.3 QUESTIONNAIRE

3.3.1 Questionnaire, Study I

The questionnaire and two reminders were sent by mail to both groups. The questionnaire was also available on the internet. Questionnaires to the patient and control groups were identical except for the questions about CD. The questionnaire contained 36 questions, including questions about socio-economy, dental care habits, oral health, general health and tobacco use. Most questions in the study were of the multiple-choice type.

The CD patients were asked to estimate the severity of their bowel disease from 1 to 10. Both groups were asked to estimate their oral health as compared to others at the same age. The alternatives offered were “Much better”, “Similar, “Worse”, “Much worse” or “Don’t know”. Similarly, they were asked to estimate their need for dental care with the alternatives “Very large”, “Large”, “Moderate”, “Small” and “Don’t know”. The question “Does your gingiva bleed?” had three response alternatives, “Yes”, ”Yes, but only when I brush my teeth”, and ”No”. The two yes responses were collapsed into one “yes answer”. The participants were also asked if they had periodontitis and were given three alternatives, “Yes”, “No” or “Don’t know”. The questionnaire also include questions about smoking habits and if they had been former smokers, and smoking was quantified by the number of cigarettes smoked per day. The CD patients were asked if they had changed their diet when they got CD, the alternatives were “No”, “Yes, I eat more often” and “Other changes”, with an opportunity to explain those changes.

3.3.2 Questionnaire, Study II and III

All participants completed a questionnaire that covered demographic data, including age, gender, income, education level, medical history, medications, and smoking habits. Most of the questions in the questionnaire were of the multiple-chose type. Several questions were based on the questionnaire from *Study I*. Smoking habits were reported as current smokers, former-smokers and never smokers, the response alternatives were yes or no. Questions concerning oral hygiene practice, included frequency of tooth brushing, interproximal cleaning, and visits to the dentist and/or dental hygienist. The questionnaire included questions cornering dental health, if during the last 12 months there had reported any toothache, dry mouth and bad breath, and if they had any problems with oral ulcerations. The response alternatives to these questions were yes or no. In addition, all participants were asked about eating habits, including frequency of meals and consumption of sweetened drinks between meals. The patients with CD were also asked how long they have had their disease, and if they had undergone any surgical procedure.

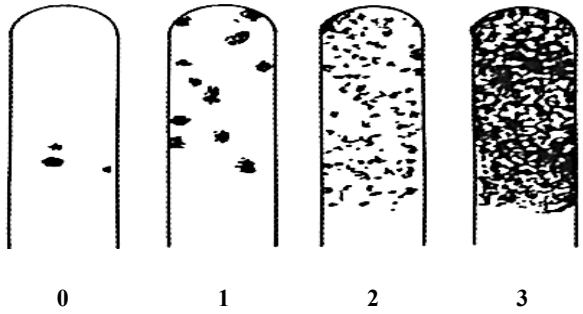
3.4 SAMPLING AND SALIVA ANALYSIS

3.4.1 Saliva Sampling

Subjects were instructed to not to eat, drink, smoke or brush their teeth one hour before sampling to avoid contamination of the oral cavity as a result of food intake or smoking. Before the clinical examination, unstimulated whole saliva and saliva stimulated by chewing paraffin wax was collected during a five minute period. Salivary flow rates were measured in milliliters per minute immediately after collection.

3.4.2 Analyzes of *Lactobacilli* and *Mutans streptococci*

Mutans streptococci (SM) counts were measured with Dentocult ® SM Strip Mutans, Orion Diagnostica. Bacitracin disc was place in the selective culture broth 15 minutes before samplings. The patients were instructed to chew a paraffin pellet for one minute before swallowing and the strip was pressed on patients tongue and removed through gently closed lips. The strip with saliva was attached to the cup and incubated at 35 to 37° C. The cup was open one quarter of a turn. After 48 to 96 hours the bacteria density on the strip was compared to the model chart (Figure 8). Salivary *Lactobacillus* (LB) counts were measured using Dentocult ® LB, Orion Diagnostica. The tube with stimulated saliva over both agar surfaces was incubated for four days in 36 ± 2 °C. The colony density was compared with the model chart, after the incubation (Figure 9). The salivary level of *Mutans streptococci* and *Lactobacilli* was measured according to the manufacturer´s instruction and expressed as colony-forming units/millilitre saliva (CFU/ml).



Class 0= <10 000 CFU/ml; Class 1= <100 000 CFU/ml; Class 2= 100 000 – 1 000 000 CFU/ml, Class 3= >1 000 000 CFU/ml

Figure 8. Model chart. *Mutans Streptococci* growth expressed as bacteria colony-forming units/milliliter saliva (CFU/ml). High number class 2 and class 3. Adapted from Dentocult ® SM Strip mutans, Orion Diagnostika OY.

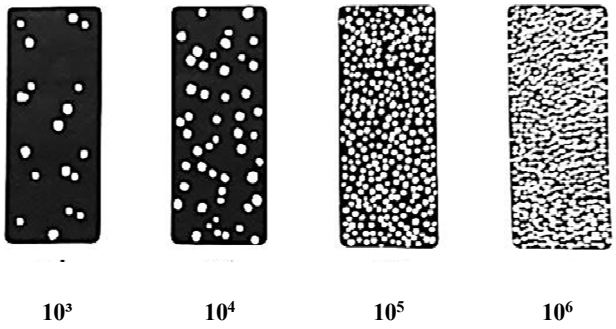


Figure 9. Model chart. *Lactobacilli* growth, expressed as bacteria colony-forming units/milliliter saliva (CFU/ml). Low numbers <1 000 CFU/ml saliva. High numbers >10 000 CFU/ml saliva. Adapted from Dentocult ® SM Strip mutans, Orion Diagnostika OY.

3.5 ASSESMENT OF ORAL HEALTH

3.5.1 Clinical Examination

Two investigators (SS/193 subjects, NR/32 subjects) made the oral and the radiographic examination of the participants in *Study II* and *Study III*. Prior to the clinical examination, an inter and intra operator calibration between the two examiners was conducted. Three participants from CD group were examined by both investigators to reach an agreement. In addition, repeated measurements within two patients were done by the same examiners. The clinical examinations were conducted after saliva sampling, registration of the number of remaining teeth and assessment of Visible Plaque Index, (VPI)[130] at six sites on all present teeth, excluding third molars.

3.5.2 Examination of Dental Caries

Caries Registration in *Study II* was assessed by WHO [131] methods and expressed by decayed, missing, or filled tooth (DMF-T) and surface index (DMF-S) in each person. The diagnosis was based on a clinical inspection, visually and tactically with an examination probe and following bitewing x-rays. Clinically, caries was recorded when a lesion had a cavity, undermined enamel or an obviously softened surface, or the probe became stuck by using light pressure. Filled surfaces with caries were registered as both decayed and filled.

3.5.2.1 The radiographic examination

The radiographic examination was done with bitewing radiographs. All tooth surfaces that could not be evaluated clinically were evaluated by the radiographs. Dental caries on the radiographs was recorded if the lesion reached the dentin. The examiner of the radiographic images was blinded, an intra-examiner measurement analysis was performed in 10% of the randomly selected patients and controls, with the measurements reaching identical results in 89% of the cases.

3.5.3 Examination of Periodontal Disease

Periodontal examination in *Study III* included registration of bleeding on probing (BOP)[132], probing pocket depth (PPD) and clinical attachment level (CAL) on six sites on all present teeth, excluding third molars, using a periodontal probe (Hu-Friedys® PCPUNC 15, Chicago, IL, USA). The presence of periodontitis was defined as having mean CAL ≥ 3mm at all sites.

3.5.3.1 The radiographic examination

The radiographic examination comprised of four bite-wing radiographs. Alveolar bone loss on the x-ray was gauged in pixel, from the mesial surface of second molars to the distal surface of canine teeth. Alveolar bone loss was measured from the cemento-enamel junction (CEJ) to the most apical part of the alveolar bone. Teeth with indistinct CEJ were excluded. The alveolar bone level on the radiographic images was studied by one examiner, who was calibrated and blinded the test and control group.

3.6 DATA ANALYSIS

3.6.1 Study I

Odds ratios (ORs) were calculated with a multiple logistic regression adjusting for age, smoking, gender and education. The significance of the differences between groups was calculated with Chi-Square, Students unpaired *t* test or Mann-Whitney *U* test. Correlation between severity of CD, oral health and dental care needs was calculated with Spearman partial correlation, adjusting for age and smoking (Table 1).

3.6.2 Study II

Data analyzes were performed using the software package PASW Statistics 18 (PASW Inc., Chicago, IL, USA). Significance of the demographic differences between patients and controls were calculated with ANOVA and variables with only two factors were calculated with Chi-square test. Post hoc analyzes were done with Fischers Least Significant Difference test or Chi-square. Analysis of covariance (ANCOVA) to control for age, gender and smoking were performed to compare the clinical variables between the groups, post hoc analyzes were done with Fishers Least Significant Difference test (Table 1). P-values of 0.05 or below were considered significant. Non-parametric data were normalized with a logarithmation. Non-parametric Spearman's correlation matrix coefficient was estimated between clinical variables and disease duration.

3.6.3 Study III

The significance/P-values of differences between CD patients and controls were calculated with Students independent samples *t*-test for age and number of missing teeth. For all other variables Pearson Chi-Square test were used. Statistical comparisons used a General Linear Model with group, gender and smoking as factors and age as a covariate, (Table 1). Analyzes were performed using the software package PASW Statistics 18 (PASW Inc., Chicago, IL, USA).

Table 1. Summary of studies.

	STUDY I	STUDY II	STUDY III
TOPIC	Perceived oral health in patients with Crohn´s disease	Dental caries, prevalence and caries risk factors in patients with Crohn´s disease	Prevalence and severity of periodontal disease in patients with Crohn´s disease
TYPE OF STUDY	Quantitative	Quantitative	Quantitative
DESIGN AND METHOD	Questionnaire	Cross-sectional (case/ controls) Clinical examination and questionnaire	Cross-sectional (case/ controls) Clinical examination and questionnaire
MATERIAL	1598 Patients 748 Controls	150 Patients 75 Controls	150 Patients 75 Controls
DATA ANALYSIS	Chi-Square test, Student´s unpaired *t*-test, Mann-Whitney *U*-test. Spearman partial correlation.	ANOVA, ANCOVA, Chi-Square test, Fischer Least Significant Difference test. Non-parametric Spearman's correlation matrix coefficient.	Student`s independent samples *t*-test, Pearson Chi-Square test. General Linear Model.
ETHICAL APPROVAL	*No required 2006*	*Dnr. 2007/2:11 & 2009/1953-32*	*Dnr. 2007/2:11 & 2009/1953-32*
PRESENTED	Riksstämman, Göteborg. Sweden, 2007 First national PhD Student Conference in Oral Science, Huddinge, Sweden, 2007 IADR, Toronto, Canada, 2008Nordic PhD Conference in Dentistry, Lillehammar, Norwegian, 2009	Riksstämman, Stockholm, Sweden, 2009 ISDH, Glasgow, England, 2010	IADR, Cape Town, South Africa, 2014
STATUS	Published	Published	Submitted

4 RESULTS

4.1 STUDY I

Patients with CD in estimated their oral health to be poorer compared to others in the same age group, with en OR of 9.7 (95% CI, 5.8 to 16.4). CD patients reported a greater need for dental treatment than the controls, with an OR of 5.7 (95% CI, 4.2 to 7.9) after adjustment for age, smoking, gender and education. We found also a correlation between the more severe forms of CD and oral health ($R=0.31$, $p<0.001$) and more dental care needs ($R=0.31$, $p<0.001$) after adjusting for age and smoking. CD patients reported significantly more mouth and tooth related problem such as tooth toothache, caries, gingival bleeding and ulcerations, lost or broken filling, broken crown and bridge work, halitosis and mouth dryness, compared to the persons without CD (OR 3.2, 95% CI 2.5 to 4.0). 96% of participants brushed their teeth twice daily or more. CD patients visited a dentist or dental hygienist significantly more often than persons without CD ($p<0.001$). Approximately 50 % of the participants visited dental clinics once a year. 11% percent of the patients and 2 % of the controls visited dental clinics more than twice a year (OR 8.7). Moreover, significantly more CD patients reported that they took some kind of medication (89% versus 37%, $p<0.001$), reported significantly more bleeding in the gingiva ($p<0.001$) and suffered with periodontitis ($p<0.028$) than controls. There were significantly more smokers in the patient group ($p<0.001$).

4.2 STUDY II

We found significantly a higher DMF-S score (decayed, missing, filled surface index) in CD patients who had undergone resective surgery (RS) (50.7 versus 36.5, $p=0.01$) compared to the control group after adjusting for age, gender and smoking. The result in RS group showed a weak positive correlation between disease duration and DMF-S ($r=0.374$; $p=0.01$), FS ($r=0.424$, $p=0.001$) and MS ($r=0.272$, $p=0.005$). These correlation was not found in the NRS group. The RS group also showed a higher DMF-T index (decayed, missing, filled tooth index) but the difference did not reach statistical significance ($p= 0.06$). Our analyzes demonstrated that men in the CD group had significantly more decayed teeth (DT) (2.5±3.7 versus 1.5±2.1; $p=0.05$), decayed surfaces (DS) (4.3±8.6 versus 2.1±4.1; $p= 0.05$) and more dental plaque were compared to CD women (56.4±27.1 vs. 42.4±26.1; $p= 0.005$). No gender differences were observed in the control group. CD patients shown significantly higher level of LB and amounts of dental plaque and RS group had more SM compared to the control group. Oral hygiene habits and frequency of meals did not differ between the groups. However CD patients reported significantly more frequent intake of soft drinks between the meals ($p=0.001$).

4.3 STUDY III

CD patients were shown to have significantly more BOP (50.8±25.0 versus 25.4±19.7; $p<0.001$), CAL (2.2±1.1 versus 1.4±1.2; $p<0.001$), VPI (48.9±27.6 versus 22.1±20.4; $p<0.001$) than subjects without CD, adjusting for age and smoking. Periodontitis, where

measuring as the percentage of CAL≥3 was also higher in patients than controls (22.7% versus 5.4%; p<0.001) adjusting for age and smoking. 83.9% of the patients with CD and 31.9% of the controls took medication regularly (p<0.001). 47 % of CD patients had undergone surgical treatment and 74 % had used some pharmacotherapy for CD. There were significantly more smokers in CD group than in control group (21.8% versus 6.7%; p=0.004). Men in the patients group had significantly more of dental plaque, VPI (56.1%±27.7 versus 42.9%±25.7; p=002), gingival inflammation, BOP (57.7%±24.4 versus 44.3%±23.8; p=0.003), CAL (2.5mm±1.2 versus 1.9±0.9mm; p=0.005), PPD (2.1mm±0.5 versus 1.9mm±0.4; p=0.036) , periodontitis (30.1% versus 15.6%; p=0.033) and more alveolar bone level loss (45.4pixel±19.6 versus 37.5pixel±11.8; p=0.032) compared to women in the same group adjusting for age and smoking.

5 SHORT SUMMARY AND DISCUSSION

This research was initiated by the Swedish Association of People with Stomach and Bowel Diseases (RMT) and Department of Gastroenterology and Hepatology, Karolinska University Hospital, Huddinge. Both of these institutions had received questions from CD patients regarding their poor oral health and that oral health problems had increased amongst their members. To date, few studies exist investigating the effect of CD on oral health. Since CD may have an impact on both dental caries and periodontal diseases, it was important to further investigate these associations

5.1 STUDY I

In *Study I* we used a questionnaire to investigate how patients with CD perceived their oral health. The results showed that CD patients perceived their oral health to be worse and reported a greater need for dental treatment than a control group of the same age. Our result also showed a correlation between the more severe forms of CD and oral health and more need of dental care. Furthermore, CD patients reported significantly more mouth and teeth related problems such as toothache, caries, gingival bleeding and ulcerations, lost or broken fillings, broken crown and bridge work, halitosis and mouth dryness, compared to persons without CD. Dental problems such as tooth caries, oral ulcers and dry were significantly more frequent in the CD patients than in healthy controls [133].

Earlier studies have investigated relative small sized groups and shown a higher prevalence and higher caries risk in CD patients compared to healthy controls [134-137]. Though, our study was based on a questionnaire it showed the same pattern regarding their oral health situation. Another study reported that patients with inflammatory bowel disease (IBD) had significantly more dentin caries than controls, but in that study patients with both CD and ulcerative colitis (UC) participated [138]. The oral condition in CD patients may be explained by changes in dietary habits and a higher intake of medicine. It is known that CD patients are recommended to eat more frequently in order to reduce pain and diarrhoea that could lead to increased dental caries, which has been correlated to dietary habits, like higher sugar intake and insufficient oral hygiene habits [136]. Our patients reported that they ate significantly more often during the day and had changed to a fat reduced diet, which may contain more carbohydrates, thus leading to an increased risk for caries. A questionnaire study by Russel et al. showed a positive correlation with cola drinks and the development in CD [139]. Moreover, significantly more patients in the present study reported that they were taking some kind of medication (89%) as compared to the controls (37%). Use of medication primarily the corticosteroids could be a reason to reduced saliva production. Dry mouth is another factor which can also contribute to increased caries risk since saliva is important for the remineralisation of the enamel [140].

Almost all participants, 96 %, in this study brushed their teeth twice daily or more, which could reflect the preventive strategies during the last 30-40 years in Sweden. A study from

US reported a significant higher frequency of tooth brushing, using dental floss and mouth fresheners at the disease onset in patients with CD compared to controls [133], while another study found no association regarding frequency of tooth brushing [139]. In our study we didn´t investigate use of flossing or use of breath freshener. Furthermore, visits to a dentist or dental hygienist were significantly more common in our patient group which also suggests that they are more in need of dental care. This is in similar to Singhal et al [133].

In this study patients reported significantly more bleeding from the gums and presented with more periodontitis than controls. Higher degree of periodontitis could be explained by the fact that there were significantly more smokers in the patient group. Smoking tended to develop a more severe form of CD, and have also a detrimental effect of the outcome of CD [141]. It is well-known that smoking is one of the most important risk-factors for both CD and periodontitis [24, 142]. Gingival bleeding has previously been reported in patients with active CD [143]. Earlier studies have described a tendency of more CAL in patients with IBD and a higher prevalence of periodontitis compared to the general adult population in the United States [138, 144]. In general, reports relating IBD and particularly CD to periodontal disease are few and evidence for an association between the two diseases is lacking [138, 144-146].

A strength of the present study is the low dropout rate out of the 1943 patients with CD, where 1598 (88%) answered the questionnaire and out of the 1000 controls, 748 (75 %) responded. Conversely a limitation could be that it is a questionnaire study and dependent upon self-reported oral health, therefore, less valid than findings from clinical examinations. Nonetheless, self-reported observations can be regarded as adequate for considering the relationship between perceived, real -data and general health. Another study found good consistency between self-reported and clinical observations [147].

The findings in Study 1 reported that CD patients perceived worse oral status that a control group and clinical studies are needed to confirm this relationship

5.2 STUDY II

In this study, we clinically examined CD patients and controls and we found a significantly higher number DMF-S scores in those CD patients who had undergone RS compared to the control group. The RS group showed also a higher DMF-T but the difference was not statistically significant. These results also support our findings from the questionnaire study (*Study I*). Other researchers have found significantly higher DMF-T in CD patents [129, 134-136], however they did not differ between the CD patients into surgical and non-surgical groups. On the other hand, Grössner-Schreiber et al. (2006) found no significances in DMF-S but reported significantly more dentin caries and plaque in patients with IBD, which include both CD and ulcerative colitis [138]. One explanation for the different results between the two CD groups might be that the patients, who had undergone surgery, had a more severe form of the disease. A recent study by Karczewski et al. (2014) reported that CD patients who smoked

had more frequently undergone surgery, and thus suffered from a more severe form of the disease and also required immunosuppressive therapy more often. Probably, there are several risk factors which are involved in the disease which may have an impact on oral health, and since smoking is one of the most important risk factors also for periodontal disease we found it important to divide the CD patients into a surgery and non-surgery group [141].

There was also a weak correlation between DMFs and disease duration in the surgery group, which was not found in the non-surgery group. The results from *Study 1* also supports this data where more severe forms of CD were associated with decreased oral hygiene. It could also be speculated that over the years of suffering from the disease prior to the RS the patients experienced problems with their oral health status and many caries restorations were performed. The most interesting findings from *Study II* is illustrated by the gender differences. Our analyzes revealed that men in the CD group had significantly more caries and more amounts of plaque compared to women. The reason for this is difficult to explain but one speculation might be that men in the CD group had worse oral hygiene habits, less frequently dental visits or worse dietary habits [148]. This speculation may be confirmed when analyzing the results in *Study I* from a gender perspective. In the present thesis, this has not yet been performed but is one of our planned future studies.

CD patients in this study had significantly more dental plaque compared with a controls, which could have an impact on caries development and is in accordance with earlier studies [138, 149]. The results also showed that oral hygiene habits and frequency of visits to the dentist and dental hygienist did not differ between the two groups. CD in general had higher levels of *Lactobacilli* (LB) in saliva and the RS group had also significantly higher salivary counts of *Streptococcus mutans* (SM) compared to the control group. Other studies have confirmed that patients with CD had higher numbers of these cariogenic bacteria which involved in caries activity but species differences exist [137, 150, 151].

Prevalence of caries in patients with CD could be enhanced by dietary habits. Sugar consumption could be the main reason of higher prevalence of caries in CD patients. Studies showing that patients consumed larger amounts of highly refined carbohydrates are associated with increased caries risk [136, 149, 152, 153]. CD patients in our study reported more frequent consumption of sweetened drinks between meals compared to controls and more dry mouth. Eating habits differed from the questionnaire study (*Study 1*) which reported that CD patients ate significantly more frequently than the control group. It should also be noticed that 44% of the CD patients reported that their oral hygiene had failed after they were diagnosed (*Study I*).

Our results confirmed that caries is a multifactorial disease and involve many risk factors.Further studies should focus on developing individual caries preventive programmes for CD patients. This knowledge is important since both the dental and the medical care

should be aware of and informed the patients about this risk. Since many areas face the same risk factors, collaboration with other health care professionals could be a possible way [154].

5.3 STUDY III

In *Study III*, we investigated periodontal clinical features of CD patients and compared them with a control group. Patients with CD had significantly more BOP, CAL and periodontitis than subjects without CD. The amount of dental plaque was also significantly higher in the patients group than control group.

High scores for plaque and gingivitis in IBD and CD patients have been reported in earlier studies [138, 143, 149, 155]. Plaque-induced gingivitis is the most common form of periodontal disease. The high gingivitis scores in our study corresponded to increased amounts of plaque, indicating poor oral hygiene in the CD group. This was also shown in *Study I,* where the patients reported more gingival bleeding compared to controls. As long as we do not know which individual that may develop periodontitis, gingivitis should be prevented and treated. Lang et al (2009) showed that an established gingival inflammation represents a risk factor for periodontal attachment loss and for tooth loss [7]. In the present study, there were no differences regarding oral hygiene habits between the two groups according to the questionnaire, similar pattern was found in *Study I*. Another explanation could be that CD patients had more dental plaque as a result of more frequently eating and high consumption of sweetened drinks [136, 152, 156, 157]. Additionally, CD patients may brush their teeth less effectively due to painful oral manifestations and or gingival bleeding during teeth brushing. The prevalence of oral manifestation in CD patients varies between 0.5 % and 20 % [105]. The patients in *Study I* reported higher score for ulcers, which also was confirmed in the clinical study [157].

The strength of this study is the large size cohort of 225 people, including 125 patients with CD and 75 controls, who were clinically examined. However, it also need to consider the high number of drop-outs from the study, but there was no significant differences regarding age and gender. Another limitation could be that periodontal examinations were performed by two examiners, however, inter and intra calibration between the two investigators were conducted before the examinations. Furthermore, to the best of our knowledge this study is the first to measure alveolar bone level on the radiographic image. However, the radiographic examination showed no differences in bone level between the two groups. A possible explanation could be that the radiographic measurements in our study were at two sites and measurement of CAL was at six sites on the teeth. CD patients in the present study had a higher prevalence of periodontitis, which are in agreement to Brito et al. [129]. Also, in *Study I* the patients reported more problems with periodontitis than controls, however the difference was negligible after adjusting for age and smoking habits. PPD and CAL in our CD group was almost in line with other studies [129, 144]. Furthermore, the prevalence of

periodontitis was increased but the severity was relatively small in the CD group, which is also in agreement with previous studies [129, 138, 144, 158] and does not have any major clinical implications. To note in our study, there were the fact that there are significantly more smokers in the CD group than in the control group although smoking is strongly associated with multifactorial chronic inflammatory conditions as periodontitis and CD [24, 127]. A meta-analysis found that current smoking was associated with an increased risk for CD (OR 1.76, 95% CI= 1.40-2.22)[159]. From a clinical point of view it is obvious that tobacco cessation plays an important role and has an impact on the severity of these two chronic diseases.

The present study also considered the gender perspective on all periodontal features in CD patients. Men in the patient group had significantly more dental plaque, gingival inflammation, CAL, PPD, periodontitis and more alveolar bone level loss compared to women in the same group. This was in accordance with *Study II,* where men with CD had worse clinical status, decayed teeth compared to women. Other studies have also confirmed this and found more gingival inflammation in men with CD [136, 148].

CD patients in this study have significantly more gingivitis and CAL but not more PPD and not more bone loss than patients in the control group. The reason for this could be that patients consumed more medication in general and immunomodulators in particular. On the other hand a recent study by, Schulz et al reported that medication had no influence on periodontal status but found that patients who took aminosalicylates exhibited decreased bleeding and probing [136]. In the present study, 84.0% of the patients with CD and 32% of the controls took medication regularly. The corresponding number of medication in *Study I* was 89% in the CD group and 37% in the controls. 47 % of CD patients had undergone surgical treatment and 74 % had used some pharmacotherapy for CD. Duration of CD, number of intestinal surgeries and use of medication did not show any influence on periodontal status for this population group but this association is complex and needs to be further investigated. Interestingly, a recent review of O´Sullivan (2015), showed that vitamin D has emerged as a candidate of interest as an adjunctive treatment in CD [160]. Intervention studies have suggested that vitamin D supplementation may reduce markers of disease activity in CD. Several strands of evidence suggest vitamin D as a potential anti-inflammatory therapy for conditions, such as IBD. The mechanism remains still unclear and needs to be investigated. The role of vitamin D in the periodontium has also been investigated and studies suggest that vitamin D and/or calcium intake results in reduced alveolar bone loss, gingival inflammation and/or attachment loss [161, 162].

Finally our results combined with others conclude that patients with CD, especially men, have suboptimal oral hygiene and poorer periodontal status than persons without CD, suggesting the need for increased prophylactic efforts for this group of chronically ill patients.

6 CONCLUSIONS

- Patients with CD perceived a poorer oral health status, more tooth-related problems and greater need for dental treatment than subjects without CD (*Study I)*.

- CD patients who had undergone RS had higher numbers of DMF-S score and salivary counts of *Lactobacilli* and *Streptococcus mutans* than the control group *(Study II)*.

- CD patients have poorer periodontal status with more gingivitis, periodontitis and higher plaque score compared to people without CD *(Study III)*.

- Men with CD had diminished oral health with more plaque, caries and more severe periodontal disease compared to women with CD *(Study II & III).*

- There were higher numbers of smokers in the CD group compared to the control group without CD *(Study I, II & III)*.

7 FUTURE PERSPECTIVES

The findings in this thesis indicate there is a need to develop an efficient oral care program for the patients with CD patients, particularly for men and specially focused on dental caries. Further studies may include deep interviews to investigate the oral hygiene, diet habits and also aim to optimize smoking cessation.

Furthermore, there is also a need for qualitative studies to attain a deeper understanding of CD, in terms of how the patients perceive their oral health and to identify strategies for maintenance care. Another important topic is to analyse behavioural aspects regarding why the CD patients clearly showed an increased use of tobacco compared to controls, since this is both an important risk factor for CD and periodontitis. Smoking cessation is one of the modifiable factors, where dental hygienists play an important role to promote better oral health and there are also cost effective benefits for public health. One strategy could be to use motivational counselling to explore patient's thoughts in order to create a plan of smoking cessation, as well as maintaining regular routines for oral hygiene. It is also of interest to further investigate the gender differences.

We plan to investigate the periodontal condition in CD patients more thoroughly regarding the microflora and several inflammatory biomarkers in gingival crevicular fluid and saliva, which are associated with the pathogenesis of many inflammatory diseases.

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Sincerely

Sara Szymanska

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